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An alternative marker of inflammation in parenteral nutrition: IMA

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Abstract
Aim: There is an increase in inflammation and metabolic complications in patients receiving PN. Because of inflammation and oxidative stress, an increase in IMA levels can be observed. We aimed to evaluate the effectiveness of detecting IMA and other inflammatory parameters in modulating nutritional therapy of critically ill patients.
Material and Methods: A total of 83 subjects were divided into two groups: 41 receiving PN (F:20, M:21) and 42 receiving EN (F:22, M:20). Patients over the age of 18 whose NRS 2002 score was <3, and who were followed up in the intensive care or palliative care units were included. CBC, glucose, protein, albumin, ferritin, CRP, electrolytes, and IMA levels were compared.
Results: There was a difference in CRP values in the group receiving PN compared to the group receiving EN (p=0.001). NLR and CRP/albumin were found to be higher in the PN group (p <0.05 and p <0.01). IMA levels were also found to be significantly higher in the PN group compared to the enteral group (p <0.01).
Discussion: Compared with EN, inflammation, metabolic and oxidative stress can occur in patients receiving PN. Increased inflammatory parameters and IMA levels are important in terms of additional treatment modalities to nutrition. This oxidant process can be prevented by using antioxidant support such as vitamins and minerals, emulsions containing olive oil, and omega-3 fatty acids. IMA and inflammatory parameters can be guiding as predictors of this process.

Keywords
Nutrition, Enteral, Parenteral, IMA, Hyperinflammation

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Introduction

Nutritional support for critically ill patients in intensive care and palliative care units is an important part of patient treatment and care. These patients are often prone to malnutrition due to decreased caloric intake combined with increased caloric needs because of metabolic stress. Various guidelines and recommendations have been developed by DGEM (German Society for Nutritional Medicine), ESPEN (European Society of Enteral and Parenteral Nutrition), and (ASPEN (American Society of Enteral and Parenteral Nutrition) for enteral (EN) and parenteral (PN) nutrition. Despite this, there is still debate about which is superior. However, the general opinion is that EN is the first choice if there is no contraindication [1-3].

For enteral nutrition, the gastrointestinal tract is used if its integrity is preserved. It is generally administered through a feeding tube inserted nasoenterically. The main reasons for recommending EN in the guidelines are as follows: EN is safer, has lower cost and risk of infection is fewer. In addition, since the continuity of enteral passage is ensured, intestinal atrophy is prevented and thus the continuity of the barrier function of the intestine is ensured [4].

If it is impossible to provide the patient with oral intake, EN is preferred, and if enteral nutrition is not available, parenteral nutrition is used [2]. PN is often used in patients with gastrointestinal dysfunction. There are studies showing that it supports prognosis and survival rates in this group of patients. Nevertheless, for this patient group, it is recommended to switch to enteral nutrition as soon as possible if there is intestinal integrity. As a result of prolonged PN, unwanted conditions such as atrophy of the intestinal mucosa, increased intestinal permeability and loss of intestinal integrity may be encountered [5]. As a result of disruption of the mucosal barrier, bacterial translocation, endotoxins are likely to enter the circulation, causing inflammation and toxemia. It is important to demonstrate the inflammation and to protect against this.

Albumin is a protein mostly synthesized in the liver and constitutes 25% of the total proteins [6]. It is modified during oxidative stress, ischemic attacks secondary to acidosis, and production of reactive oxygen species, free radical formation alters the ability of the amino-terminal end (N-terminal) of albumin molecule, so this altered albumin cannot bind transitional metals such as cobalt, copper, and nickel, any longer [7]. This altered type of albumin is called ischemic modified albumin (IMA). It is measured by Albumin-Cobalt Binding Test (ACT).

In recent studies, IMA has been suggested as an early biomarker for many diseases associated with oxidative stress (such as myocardial infarction, hyperthyroidism, hypothyroidism, diabetes mellitus, chronic renal failure, cerebrovascular events) [8]. It can be said that IMA is a non-specific marker of tissue ischemia induced after ischemia-reperfusion. Starting from this point of view, we thought that hyperglycemia, ischemia, inflammation, and oxidative stress due to parenteral nutrition may increase serum IMA levels besides other inflammatory markers. This can help us detect the inflammation state of receiving parenteral nutrition. In our literature review, we could not find any study comparing nutritional methods with this biomarker and evaluating parenteral nutrition in terms of inflammation. Therefore, we aimed to evaluate the effectiveness of detecting IMA levels in modulating nutritional therapy of critically ill patients.

Material and Methods

This study was performed in patients who received inpatient treatment in Elazig Fethi Sekin City Hospital intensive care and palliative service clinics and were fed with total parenteral nutrition or enteral nutrition in accordance with ASPEN and ESPEN guidelines. The patients were examined in two groups. A total of 83 subjects, 41 receiving TPN (F:20, M:21) and 42 receiving Enteral Nutrition (F:22, M:20), were included in the study. The study included patients over 18 years of age whose NRS 2002 score was <3 and who were being followed up in the intensive care or palliative care units. The exclusion criteria were as follows: patients with 1-Ischemic heart disease 2-Circulatory disorders such as peripheral artery disease 3-Diagnosis of sepsis 4-Inflammatory bowel disease 5-Rheumatologic/ immune system disease 6-Diagnosis of malignancy 7-Chronic liver disease. Demographic data such as age, gender, and comorbidities of the patients were recorded. Informed consent forms were signed by the patients or their relatives.

Our study was approved by the Ethics Committee of Fırat University and complies with the principles of the Declaration of Helsinki.

Blood samples were taken from the groups and 5ml of samples was inserted in tubes containing aprotinin (BD Vacutainer K_3EDTA/Aprotinin, Plymouth, UK). Glucose, protein, albumin, and electrolyte measurements were studied in AU-5800. Ferritin levels were studied in DxI 800 (Beckman Coulter, Inc., Miami, FL, USA). CRP levels were determined by nephelometric method on an Immage-800 protein Chemistry Analyzer (Beckman Coulter Inc., Minnesota, USA), complete blood count was analyzed on the DxH 800 device. The blood samples were centrifuged at 4000 rpm for 10 minutes and placed in Eppendorf tubes. These tubes were stored in freezers at -20°C IMA to be studied until the working day.

Plasma IMA levels were studied using the Human IMA ELISA kit (Sunred Biological Technology, catalog no: 201-12-1173, Shanghai, China) in accordance with the operating procedures specified in the kit catalog. The absorbance measurement was made on the Chromate 4300 Microplate Reader (Awareness Technology, Palm City, USA). The minimum detection limit for IMA was 2.26 μg/L. The intra-assay and inter-assay coefficients of variation for plasma IMA were <9% and <11%, respectively.

SPSS program (version 21) was used for statistical analysis. Data were calculated as mean ± standard deviation. The Kolmogorov-Smirnov test was used to find out whether the variables showed a normal distribution. Student's T-test was used for the analysis of parametric data and the Mann-Whitney U test was used for the analysis of non-parametric data. For evaluation of qualitative data, analysis was performed with the chi-square test. Also, the Spearman correlation analysis was performed to find out any relationship between the investigated parameters. Statistical differences between the means were considered significant if p-values were <0.05.

Results

The laboratory and demographic data of the study are summarized in Table 1. Forty-one of the 83 patients received parenteral nutrition and 42 received enteral nutrition. In the group that received PN, 21 were men and 20 were women. In the group that received EN, 20 were male and 22 were female. There was a significant difference in CRP values in the group receiving PN compared to the group receiving enteral nutrition (p=0.001). In addition, NLR and CRP/albumin ratios, which have become increasingly popular as an indicator of an inflammatory parameter, were also found to be significantly higher in the PN group (p <0.05 and p <0.01). IMA levels were also found to be significantly higher in the PN group compared to the enteral group (p <0.01).

A positive correlation was found between IMA and CRP (r:0.380, p= 0.014) in the PN group. There was also a positive correlation between CRP and NLR (r: 0.432, p= 0.005) (Figure1). A positive correlation was found between IMA and CRP (r:0.355, p= 0.021) in the enteral group. There was also a positive correlation between CRP and NLR in the enteral group (r:0.317, p= 0.041) (Figure 2).

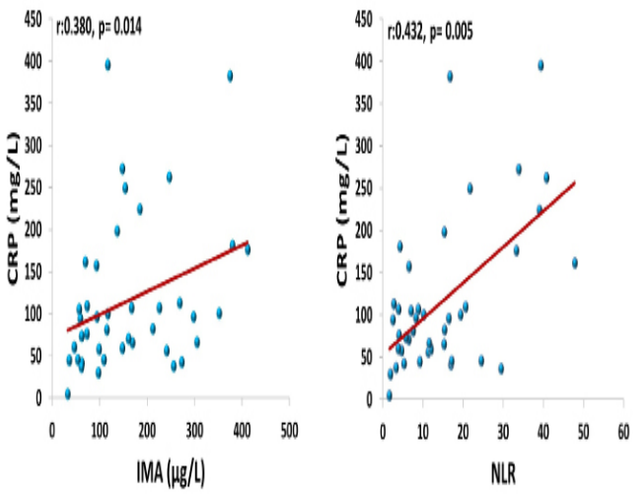

Figure 1. Correlation curves between IMA, CRP and NLR in PN group.

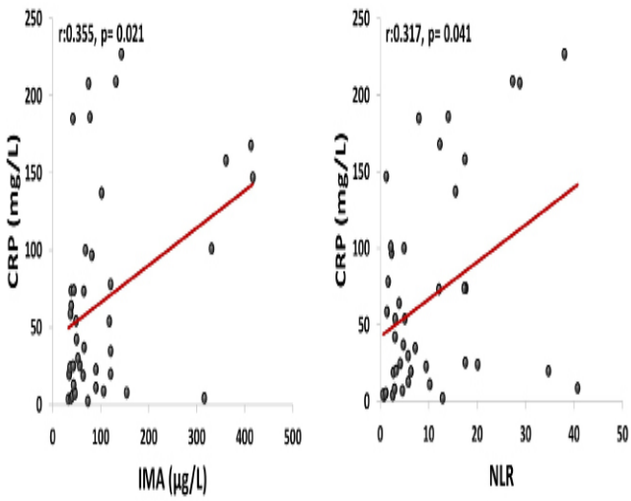

Figure 2. Correlation curves between IMA, CRP and NLR in EN group.

Discussion

Nutritional support is a routine requirement for critically ill patients, especially in intensive care and palliative care units. If timely and adequate nutritional support is not provided, energy and protein deficiency occurs [9]. This situation plays an important role in the prognosis of the patient. Problems that will arise in case of insufficient or inappropriate nutrition are as follows: a decrease in fat and muscle mass, hypoalbuminemia/ decrease in oncotic pressure, delayed wound healing, inadequate immune response, increased risk of infection, delayed recovery in surgical anastomoses, gastrointestinal, cardiovascular, and respiratory system disorders, metabolic acidosis can be observed [10].

Enteral nutrition is one of the nutritional methods. EN increases epithelial proliferation and ensures the continuity of the intestinal barrier. It reduces intestinal permeability by preventing intestinal villus atrophy. It stimulates intestinal perfusion and plays a protective role against ischemia-reperfusion injury. It has been shown in previous studies that EN prevents bacterial translocation and improves local and systemic immune response [11]. It has also been found to be more advantageous not causing metabolic problems such as hyperglycemia, water, and electrolyte disorders when compared to parenteral nutrition [12].

In cases where nutritional support cannot be provided enterally, such as short bowel syndrome, enteric fistulas, severe vomiting and diarrhea, intestinal obstruction, nutritional support is provided by parenteral nutrition. However, there are various complications of parenteral nutrition such as complications related to catheter insertion or catheter infection and metabolic complications such as hypo-hyperglycemia, metabolic acidosis, electrolyte disorders, hypertriglyceridemia, hyperazotemia, fatty liver, and liver dysfunction [13].

During parenteral nutrition, the gastrointestinal tract is bypassed. Therefore, there is shrinkage and atrophy in the villi

Table 1. Laboratory and demographic data of the groups

	PN (n:41)	EN (n:42)	p value
	Median (min-max)	Median (min-max)	
Gender (F/M)	20/21	22/20	0.827
Age (years)	65 (20-91)	77 (23-95)	0.009
WBC (10^9/L)	10.1 (3.40-34.8)	10.05 (3.2-17.7)	0.931
NLR	11.31 (1.63-47.8)	5.76 (0.6-40.7)	0.039
PLT (10^9/L)	192 (42-508)	249.5 (74-444)	0.084
HGB (g/dL)	8.9 (7.1-13.4)	10 (7.1-14.6)	0.115
HCT (%)	27 (21.6-41.7)	30.15 (20.7-44)	0.095
Glucose (mg/dL)	120 (72-238)	101 (71-423)	0.264
Na (mmol/L)	138 (131-151)	138.5 (130-160)	0.476
K (mmol/L)	3.72 (2.47-5.8)	3.67 (2.33-5.1)	0.820
Cl (mmol/L)	105 (87-116)	102.5 (90-121)	0.141
Protein (g/L)	56 (38-67)	56.5 (44-74)	0.978
Albumin (g/L)	29 (15-36)	28 (19-37)	0.568
CRP (mg/L)	94 (4.2-395)	39.5 (2.1-227)	0.001
CRP/Albumin	3.14 (0.12-15.8)	1.46 (0.1-8.73)	0.002
Ferritin (µg/L)	332 (28-1201)	234 (19-911)	0.231
IMA (µg/L)	137 (32.6-412)	66.8 (33-417)	0.002

[14, 15]. An increase in bowel permeability is observed due to cellular edema. There are studies showing increase in endotoxin and inflammation due to bacterial infiltration [16]. Monitoring of inflammatory parameters is important for the management of this situation. In the literature, CRP, WBC, NLR, Ferritin, IL6, and IL8 are mostly recommended as follow-up parameters of this process [17].

In this study, we compared enteral and parenteral nutrition in terms of increased inflammation, we found that CRP, NLR, CRP/Albumin ratios were significantly higher in patients with parenteral nutrition. We think that both the increase in inflammation due to atrophy and high permeability of the intestinal villi and metabolic complications caused this situation. As a result, we showed that the inflammatory process, which occurs with increased metabolic stress, became more prominent in the PN group. In a recent study that supports us, Stoll et al. compared newborn pigs given EN or PN. They observed increased myeloperoxidase activity and many inflammatory parameters [18].

In our study, in addition to these inflammatory parameters, we also evaluated ischemia modified albumin (IMA) level, which has been proven in many studies reflecting the oxidative stress. It has been shown that IMA increased due to high oxidative stress in ischemia conditions affecting many organs, especially the myocardium [19]. Also, IMA values were also found to be high in cases of hypercholesterolemia, hyperglycemia, cirrhosis, metabolic syndrome, oxidative stress, and hyperinflammation [20-22].

We could not find any study in the literature that evaluated the oxidative stress created by parenteral nutrition with IMA levels. The fact that the IMA parameter is not specific to any tissue and is correlated with inflammatory parameters has guided our study in terms of reflecting inflammation in patients receiving different nutritional support. We observed that IMA levels were significantly higher in the PN group. We think that increased inflammatory response caused by PN and released oxygen radicals decrease the cobalt binding capacity of albumin and increase IMA levels. Hypercholesterolemia and hyperglycemia are also common in patients receiving PN. This situation increases oxidative stress together with endothelial damage, causing an increase in inflammatory parameters and IMA value. We found positive correlations between IMA and CRP, CRP and NLR in patients receiving both parenteral and enteral nutritional support. This showed that the correlation of IMA and inflammatory parameters can be used to indicate oxidative and metabolic stress for both groups. The fact that CRP, CRP/Albumin and NLR levels were significantly higher in the PN group compared to the EN group indicates that inflammation is higher in this group. Therefore, we concluded that the patients in this group were under higher metabolic stress and oxidative load.

Due to this increased inflammation in patients receiving PN, lipid emulsions have gained importance because of their energy source and anti-inflammatory effects [23]. Olive oil-based emulsions and Omega-3 fatty acids have shown beneficial effects on cellular defense and inflammation [23,24]. Besides, various vitamin and mineral supplements are also used in patients with PN due to their antioxidant properties. In our study, increased inflammatory parameters and high IMA values as an indicator of oxidative stress in patients receiving PN are of great importance in terms of additional treatment modalities to nutrition.

Conclusion

Inflammation, metabolic and oxidative stress that occur in patients who receive PN cause negative consequences in the treatment process of these patients. This oxidant process can be prevented by using antioxidant support such as vitamins and minerals, emulsions containing olive oil, and products containing omega3 fatty acids. IMA and inflammatory parameters can be guiding as predictors of this process.

Limitations

One of the limitations of our study is that it is a single-centered study and the sample size is small. In addition, the patient group in our study was performed in intensive care and palliative care units, and the mortality of the patients is high due to their comorbidities. For this reason, the fact that the patients could not be given antioxidant support and control blood values could not be observed is another limitation.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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